Precision medicine: hype or hope?

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I recently attended the 10th Annual Harvard Personalized Medicine Conference. One presentation at this meeting was preceded by a video outlining the course of a patient who was diagnosed 4 years earlier with a stage IV non–small cell lung cancer—a diagnosis that normally would portend a 6-month survival. However, this woman who never smoked had an *EGFR* mutation, which predicted a longer response based on treatment with erlotinib, a drug that inhibits the pathway activated by the *EGFR* mutation and was not approved by the Food and Drug Administration until May 2013 (1, 2). She was treated on a clinical trial with erlotinib and had a remarkable response. However, a year later, her tumor developed resistance to this drug because of a second mutation. This is a common scenario that oncologists frequently experience. A few years ago this woman would have never made it to this point, since we had no drugs to effectively treat her at the outset.

This case was especially poignant for me since my wife and I experienced the exact same scenario in 2008 and 2009. My wife had a cough, which was initially thought to be pneumonia. However, a computed tomography (CT) scan *(Figure 1a)* showed a mass, mediastinal adenopathy, and a pleural effusion. A bronchoscopic biopsy diagnosed an adenocarcinoma. My extreme depression was somewhat alleviated when I found out that she expressed a mutation in exon 19 (L747-A750 deletion) of the *EGFR* gene. I knew that we had a chance for a prolonged response, and I hoped that if our remission lasted long enough, the explosion of scientific discovery that was occurring in this field might actually produce a cure (a hope that most patients have). The first part of my dream came true. The first CT 7 weeks after starting erlotinib *(Figure 1b)* showed a near complete response, and her brain metastases had disappeared with just one erlotinib tablet per day. However, a year later she developed a T790 mutation, which caused the erlotinib to be ineffective (3). No new drug had been developed, and she died. It was bittersweet for me to watch the video shown at Harvard's personalized medicine meeting. Thankfully, the woman in the video had her carcinoma a couple years later than my wife. In that interval, new drugs had been developed, which this woman was able to get through a clinical trial.

A panoply of clinical trials exists with these new therapies that are being developed at an amazing pace. Unfortunately, even though these trials offer the possibility of life-prolonging results, as was evidenced in this woman in the video, most physicians do not offer these trials to their patients. This woman in the video obtained another complete response, which she is still enjoying 4 years later. I doubt that she is cured, but she is getting closer, and another drug may come along before she has her next recurrence. Since this woman's last drug was made available to her, the science has mushroomed at an even faster pace with the development of next-generation sequencing, RNA sequencing, metabolomics, and other building blocks of systems biology that identify for physician-scientists the mutations that are really important for the patient they are treating. If my wife's illness had started 5 years later, my grandchildren would still be enjoying their loving and fun grandmother.

What has allowed these amazing therapies to develop? The answer is discovery of disease mechanisms through an investment in research. The groundwork was laid in the 1980s with the development of the polymerase chain reaction, which allowed expanded research on DNA and brought genetics into the modern era (4). This led to a much better understanding of what drives the growth of tumors and gave oncologists targets to develop much more effective and directed therapies against. The science and therapies have not been limited to oncology. Examples include ivacaftor (5) to treat type 3 cystic fibrosis, L-dopa to treat Segawa's dystonia (6), and the 12/14 translocation to define people at risk for sudden death because of the long QT interval (7), to name just three. Medicine, and especially oncology, has entered a new era. But what is the real promise of this new era in medicine? The stories enumerated above are amazing and could not have been told 10 years ago.

However, we do not know the targets for most of the diseases that we see, and in oncology we have an especially difficult problem. After we discover an effective drug against a driver mutation, the tumor will usually discover a way around

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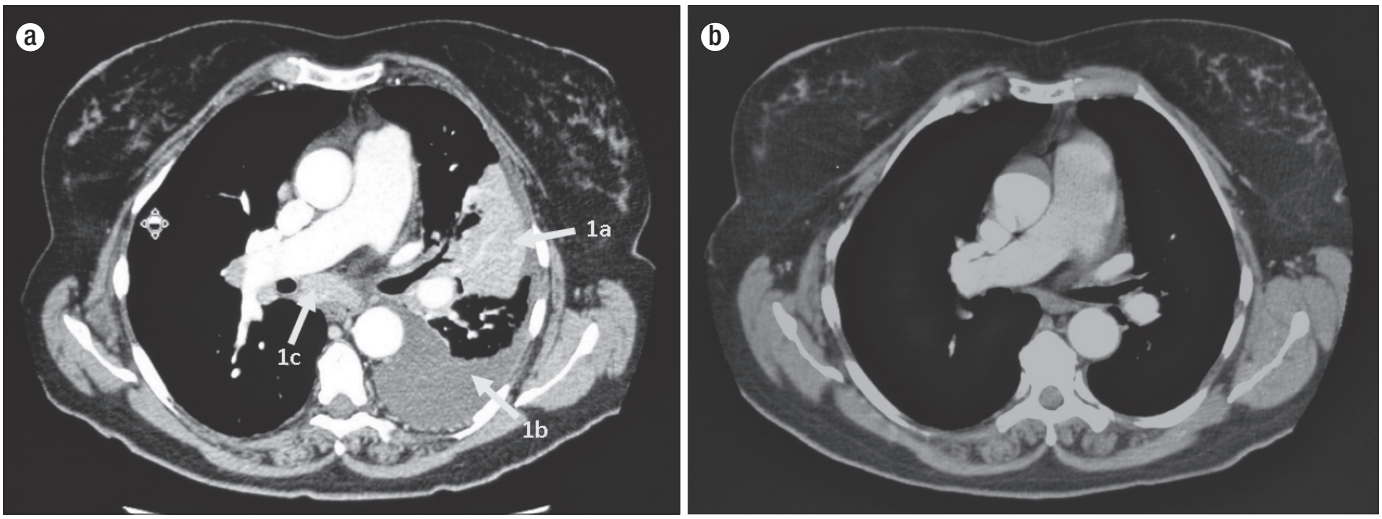

Figure 1. (a) The initial CT scan showing the left lung mass (1a), a pleural effusion (1b), and mediastinal adenopathy (1c). **(b)** The CT scan after 47 days of erlotinib showing near complete resolution of the pathologic findings.

our therapy, as was demonstrated in my wife's case. This leaves oncologists and their patients at the point that they started a number of months earlier. This scenario should not be a surprise, since there are many different metabolic pathways in the cell. Let me ask a simple question: If you had a specific route to work and one day the route that you normally took was blocked, would you be able to find your way to work? I think you would, since it is a rarity to have only one way to get to any destination. *Figure 2* shows some of the pathways in a cell used by tumors for growth. Think of this as a roadmap. If our drug blocked one growth pathway, don't you think that the tumor would find another pathway for growth, like you would find another route to work?

Have we made progress? Yes, without a doubt we have made remarkable progress! Where do we need to go from here? Straight ahead! We need to stay the course or, better yet, chart a new course. As director of the Baylor Precision Medicine Institute, I have a very vested interest in precision or personalized medicine. I honestly think that the principles of precision medicine will change the practice of medicine to a much greater degree than it has already. However, there are a number of obstacles to the promise of precision medicine. These obstacles are the expectations of patients and physicians, the culture of physicians, and the ability to do the needed research.

Precision medicine needs to simultaneously increase and decrease the expectations of patients and physicians. The examples that I have given above will excite patients and physicians alike. However, this excitement will lead to unrealistic expectations of what precision medicine can accomplish right now, at this point in history. If precision medicine cannot produce now what people are expecting it to produce, precision medicine's development will be delayed. We cannot promise what we cannot deliver now. Therefore, we need to simultaneously curb the enthusiasm about what precision medicine can produce at this time, while increasing the enthusiasm over what precision medicine will eventually deliver in the future. The potential accomplishments of precision medicine are without bounds. Five years ago, there was virtually no effective therapy for metastatic melanoma. Now we have ipilimumab, *BRAF* inhibitors, *MEK* inhibitors, and PD-1 and PD-L1 inhibitors. The four images in *Figure 3* show remarkable responses that occurred during the vemurafenib trial. These results, which would have never been witnessed 2 years before, are so exciting that patients and physicians may interpret them as cures. They are not usually cures. However, they are probably the first steps on the journey to cure most disease. They are the first steps on the research journey.

Research is the paramount event that will allow precision medicine to reach its full expectations. Research may also delay the development of precision medicine. These two statements frame a paradox. If we sequence a person's genome, we will find thousands of mutations. However, we will know what to do with <1% of them. The remaining 99% comprise the basis for the basic and clinical research that is needed to advance precision medicine. This delineates the enormity of precision medicine's task. This research is expensive, and research dollars are being cut back. How are we going to pay for this research? There are more questions than investigators and patients to answer these questions. Where are the investigators and patients going to come from? How are we going to frame the most important questions to be answered and convince investigators to cooperate in answering these questions? The gold standard for clinical research is the randomized controlled trial. If you have a drug against the driver mutation or its products causing the disease, is it ethical to do a randomized controlled trial in a group of patients with this driver mutation? The precision medicine community needs a coordinated plan to approach all of these questions. This organized approach is needed in a medical research community that prefers to work independently, is very protective of its data, is not likely to freely share data, generally lacks banked biologic data to answer questions, and for the most part does not have adequate informatics to solve their problems. This is

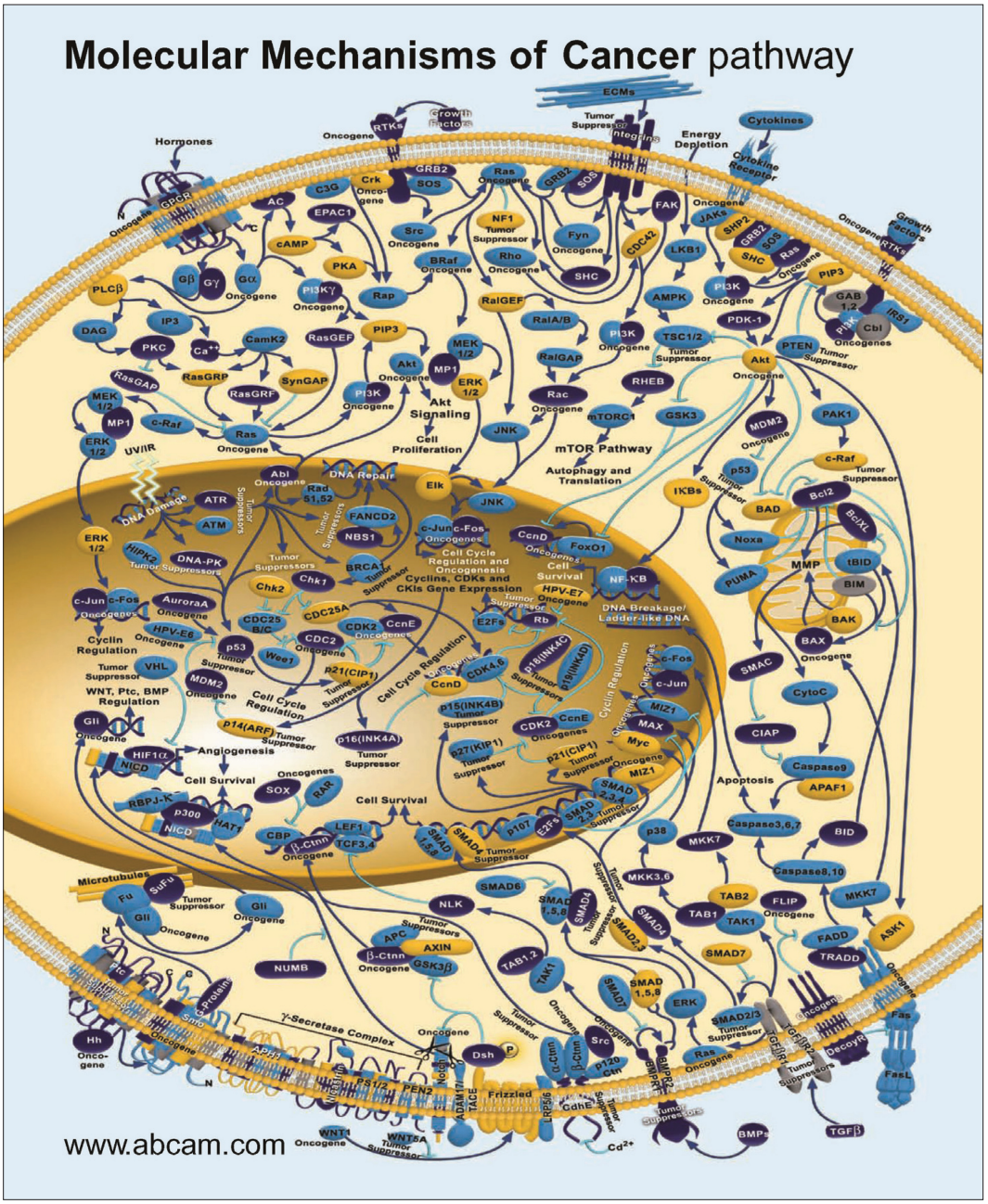

Figure 2. A simplified representation of a cell's proliferation pathway. Image courtesy of Abcam.

an enormous but surmountable problem for precision medicine that needs to be solved.

The culture that physicians practice in is another obstacle to the implementation of precision medicine. Most physicians are not fluent in the principles of precision medicine. Research in precision medicine will take more time than the standard care of patients. This will require a culture change for all of us. Medicine has made amazing progress in the 45 years that I have been a physician. But if we are honest with ourselves, we do not have the answer to most of the diseases that we treat. Therefore, research is necessary.

We need to stay our course in very unfriendly waters, continuing the basic research and translating these findings into new diagnostics and new therapies. We need to do this in an era where research funding is decreasing and where most patients are not enrolled in clinical trials but are treated with standard, often ineffective therapies. As physicians, we need to be honest with ourselves and recognize areas where our therapies are inadequate; if our patients still want therapy, we need to find trials that make sense and not continue to treat them with therapies that usually do not work. This is easy to say but difficult to do. Precision medicine can deliver amazing results now, but the promise for even greater results in the future is huge. In order to reach this prediction for precision medicine, we as physicians need to use the science that is available, encourage and participate in basic and clinical research, and ask ourselves whether the therapies that we are using are effective or ineffective and in need of a new treatment paradigm.

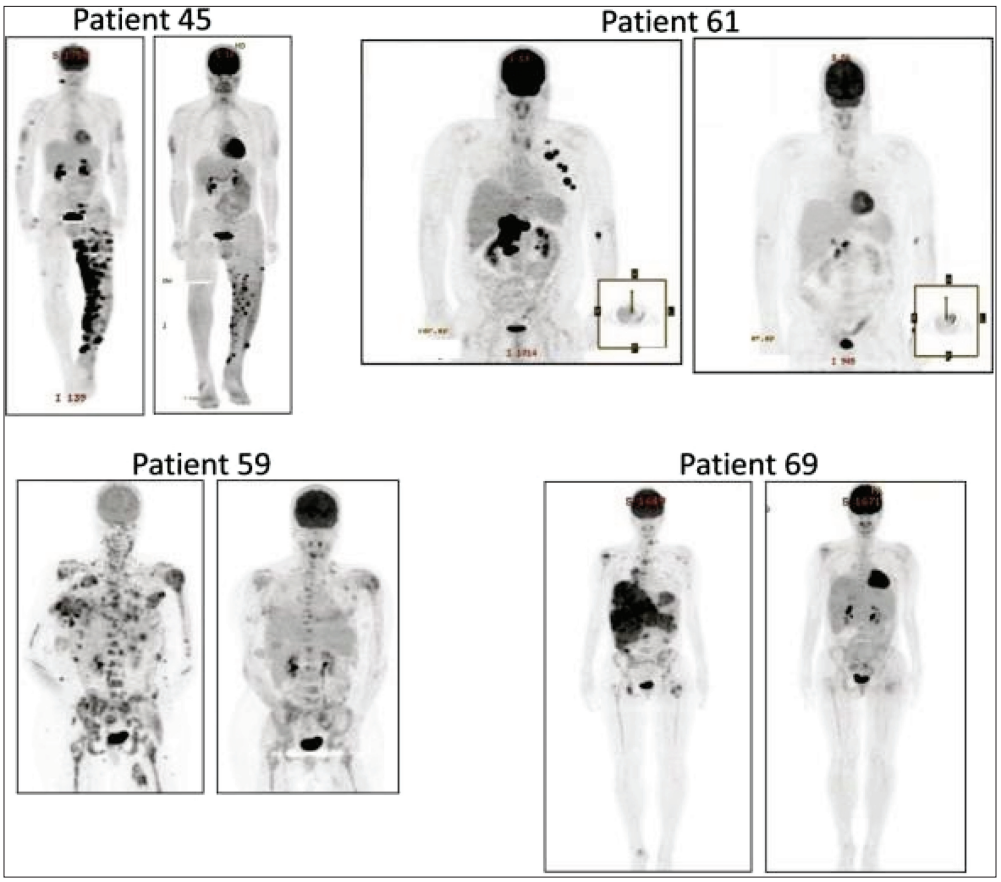

Figure 3. Positron emission tomography scans before and after vemurafenib therapy showing the dramatic response with the early use of this drug.

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